Considerations for Oncology Clinical Trials

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Overview

- A. Oncology Clinical Trials: What is the difference?
- B. Oncology trials design
- C. Oncology trials Endpoints
- D. Challenges and new trends

A. Oncology Trials: What is the difference?

What is Different About the Disease?

- Many cancers are life-threatening.
- Many cancers neither curable or controlable.
- Malignant disease implies limited life expectancy
- Different perspective on serious adverse events

What is Different About Treatments?

- Mostly invasive
- Chemotherapy
- Radiation Therapy
- Immunotherapy
- Biomarkers, diagnostics, screening
- Time demanding
- More Involvement of family and care takers
- Many involve combination therapy

Treatments Approaches: Immunotherapy

- **Immunotherapy** aim to harness the body's natural immune response to fight cancer. Three general categories:
  - checkpoint inhibitors, which disrupt signals that allow cancer cells to hide from an immune attack;
  - cytokines, protein molecules that help regulate and direct the immune system;
  - cancer vaccines, which are used to both treat and prevent cancer by targeting the immune system.

Treatment Approaches: Biomarkers

- **Biomarker**: a characteristic that is objectively measured and evaluated as an indicator of normal biological, pathogenic processes or pharmacological responses to a therapeutic intervention.
- Applied to the detection, screening, diagnosis, treatment and monitoring of cancer.
- Often used with targeted therapy.
- Developing therapies that can target the biomarker can minimize the risk of toxicity and reduce the cost of treatment.
- Genetic abnormalities often underlie the development of cancer.
- Certain DNA or RNA markers may therefore help in the detection and treatment of specific cancers.

Treatments Approaches: Targeted Therapy

- Targeted therapies:
  - Drugs or other substances designed to block the growth and spread of cancer by preventing cancer cells from dividing or destroying them directly.
  - While standard chemotherapy affects all cells in the body, targeted therapy directs drugs or other specially created substances to attack cancer cells.
  - Interfere with genes or proteins involved in tumor growth to block the spread of the disease.
  - Targeted therapy reduce the harm to healthy cells.
  - Serve as the foundation for precision medicine, shifting the focus from average patient to precise therapy.

Investigators, Users, and Approaches

- Investigators/ sponsors: Cancer Centers, Cooperative Groups, NCI, Industry, combination of sponsors
- Users: Many products used by oncologists, chemotherapist, Radiation therapists,

  others who use biotherapy, devices, supportive care, diagnostics and delivery media
- Multidisciplinary approaches
- Over 100 diseases/indications

Regulatory Prospective

- Acceptance of higher degree of toxicity
- Acceptance of single trial rather than 2 or more trials
- Acceptance of uncommon development strategies like frequent use of accelerated pathway
- Acceptance of surrogate endpoints.
- Considers more issues other than safety or efficacy such as:
  - available therapy, indication, disease,
  - state of science, regulatory precedence

B. Oncology Trials: Design

Traditional Clinical Trials Design

PHASE I: maximum-tolerated dose assessment

PHASE II: response signal

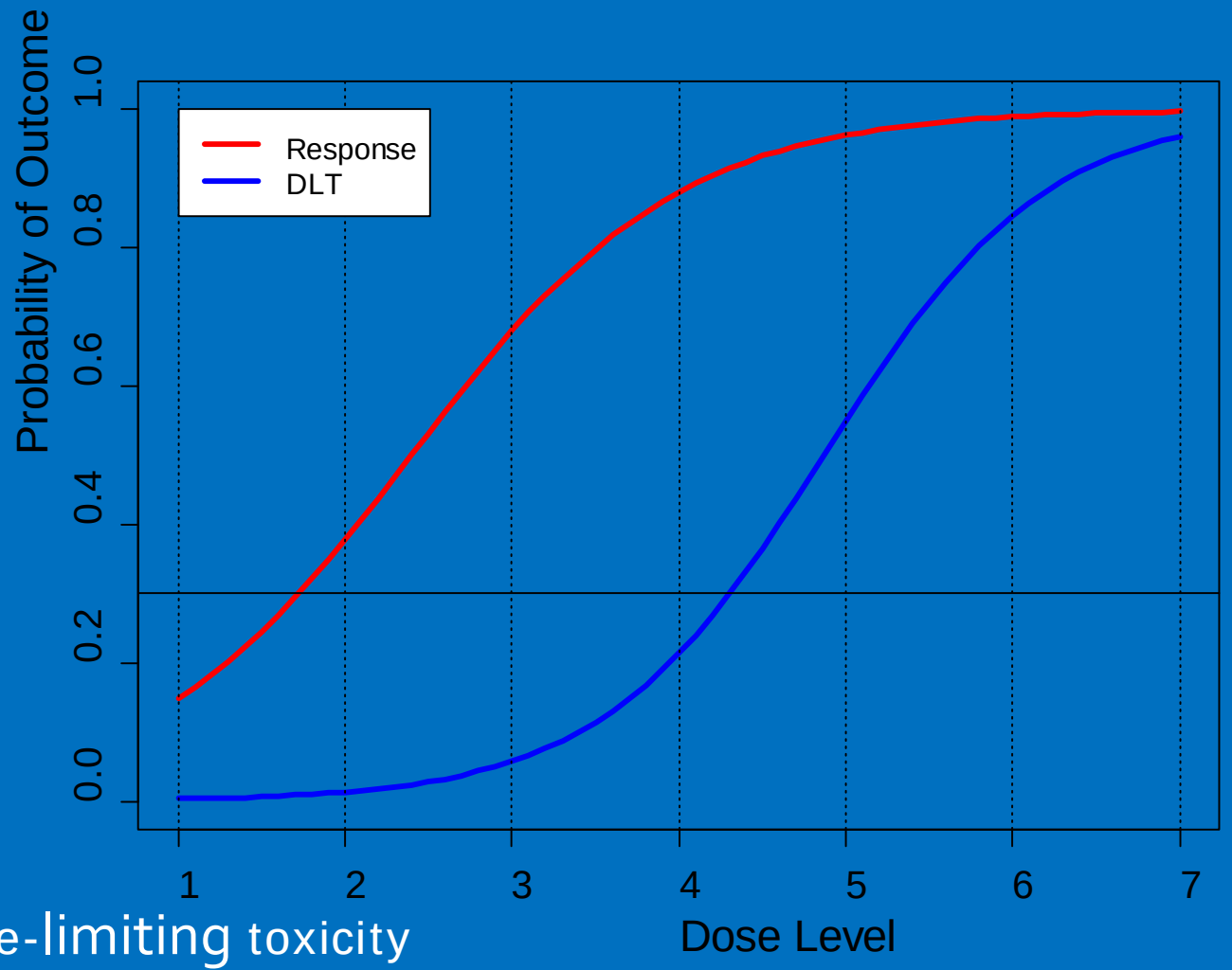
PHASE III: comparison to the standard or added to the standard

Phase IV: post marketing/approval

Those are known as intervention/trials and will be the major topic of talk

Including new trends .

Efficacy & Toxicity both Increase with Dose



DLT = dose-limiting toxicity

Other Types of Clinical Trials

- Natural History: A prospective study to determine the natural course of cancer when left untreated or Treated with standard Therapy
- Prevention (Chemoprevention):Evaluate the effectiveness of ways to cancer risk reduction.
    - Enroll healthy people at high risk for developing cancer
- Diagnostic: Develop better tests/procedures to early identify a suspected cancer or more accurately using Imaging tests and/or Lab correlative studies/tumor marker

Other Types of Clinical Trials

- Supportive Care/QOL: Evaluate improvements in comfort or QOL
  - For cancer patients and families and caregivers.
- Imaging: Understand if/how an imaging test best used to
  - Screen, diagnose, direct the treatment of/or monitor response to a therapy for a disease (e.g. SBRT)
- Screening and Early-Detection: Assess new means of detecting cancer earlier in asymptomatic people
  - using: Tissue sampling/procurement , Laboratory tests, genetic testing Imaging tests , Physical exams, and history

C: Oncology Trials: Endpoints

Endpoint Selection

The decision should always be related to:

- The patient subpopulation of interest
- The stage of disease (depends on the type of cancer)
- The characteristics of the treatment (toxicity, efficacy)
- The aims of trial (superiority/non-inferiority/safety)
- The other treatments already available to that group of patients
- Ethics
- Practical feasibility (costs, logistics…)

Characteristics of a Good Endpoint?

Relative: Clinically Important

Valid: Measures the intended effect

Reliable: Same effect produce consistent measurements

Objective: interpreted effect yields consistent measurements

Specific: Unaffected by extraneous influence

Precise: Low variability

Quantifiable: Has appropriate scale

Sensitive: Responds to small change

And account for : Cost, time, tradition, population

Phase I Endpoints- Toxicity

- Most important are DLT and MTD
- Typically DLT defined at the first cycle/course of treatment
  - >= Grade 3 non-heme toxicity: (Most common: Fatigue & other constitutional symptoms, Rashes & other skin effects, Infection, Effects on vision, Nausea & Vomiting)
  - Grade 4 : Neutropenia lasting longer than 5 days
  - Grade 4 : Thrombocytopenia
- MTD : Highest dose level with maximum one 1 out of 6 patients develop DLT

Some Efficacy Endpoint Definitions

- Overall survival (OS): Time from randomization until death.
  - May included deaths due to other causes.
- Disease-Free Survival (DFS): Randomization until tumor recurrence or death from any cause
- Objective Response Rate (ORR): Proportion of patients with reduction of tumor size of predefined amount and for a minimum time period = PR+CR
- Progression Free Survival (PFS): Randomization until tumor progression or death
- Time to progression (TTP): Randomization to progression, excluding deaths
- Time to treatment Failure (TTF): Randomization to discontinuation of treatment for any reason- not recommended for approval

RECIST (Response Evaluation Criteria In Solid Tumor) Version 1.1

Objective assessment of tumor size.

- At baseline, tumor lesions/lymph nodes categorized into:
  - 1. Measurable: Must be accurately measured in at least one dimension with minimum size (see guidelines for specifics)
  - 2. Non-measurable: all others including small lesions (longest diameter <10mm or pathological lymph nodes with ≤ 10 to <15mm)
  - The guideline lists specifications by methods of measurements and assessments.

RECIST: Target Lesions

Up to 5 measurable lesions (and max of 2 lesions per organ) are identified as target lesions.

Response criteria for Target lesions:

- Complete Response (CR): disappearance of all target lesions or reduction of lymph nodes short access to < 10mm.
- Partial Response (PR): at least 30% decrease in the sum of diameters of target lesions compared with baseline
- Progressive Disease (PD): at least 20% increase in the sum of diameters of target lesions compared with the smallest sum such that the absolute increase >= 5mm. Or appearance of new lesion.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD compared to the smallest sum diameters while on study.

RECIST : Non-Target Lesions

Response criteria for Non-Target lesions:

- Complete Response (CR): disappearance of all non-target lesions and normalization of tumor marker level. Reduction of lymph nodes short access to < 10mm.
- Non-CR/Non-PD: Persistence of one or more –non-target lesion and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): at least 20% increase in the sum of diameters of target lesions compared with the smallest sum such that the absolute increase >= 5mm. Or appearance of new lesion.

The Gold Standard: Overall Survival

- Advantages:
  - Most relevant to patient
  - Clear and accurate endpoint
  - Usually easy to get this information
  - It is easier to decide upon a treatment when its impact on survival is known
  - Assessment in earlier disease stages
  - Impact on drug development in general

The Gold Standard: Overall Survival

- Disadvantages:
  - Affected by competing causes of death
  - Longer trials
  - Larger sample sizes.
  - Influenced by post-trial therapy
  - Expensive

Surrogates in Drug Approval

- Surrogate endpoint definition*:
  - Substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives.
  - Changes are expected to reflect changes in a clinically meaningful endpoint.

(*Temple RJ, Clinical Measurement in Drug Evaluation. Nimmo and Tucker. John Wiley & Sons Ltd, 1995.)

- It should be validated via:
  - Meta-analyses of clinical trials data
  - Comprehensive understanding of:
    - The causal pathways of the disease process
    - Should correlate with clinical outcome
    - The intervention's intended and unintended mechanisms of actions.

Specific-Time Progression Endpoint

- Progression at a specific time point ,T (e.g. 6 months)
- In addition to baseline data, we need to document progression before T or stable disease at T.
- It requires less data collection and minimize time-related bias
- You know when you can stop and evaluate
- Easy to use with two-stage designs
- But has the potential loss of statistical power.

Primary Endpoint Selection

Endpoint	Advantages	Disadvantages
Tumor RR	Standardized, easily applicable to multicenter trials Early outcome	Measurement imprecision Difficult in some tumor types (mesothelioma and peritoneal disease) Correlation with patient benefit variable
TTP, PFS	Unlike OS, not confounded by salvage therapy	Subject to assessment and investigator bias Requires control cohort Only partially validated as a surrogate of survival benefit
OS	Clinically relevant outcome	Requires control cohort Affected by crossover designs and subsequent therapies Longer follow-up time required
Quality of life	Indicative of direct patient benefit	Multiple comparisons may lead to positive results by chance Time-intensive evaluation Analyses complex
Molecular biomarkers	May prove to be predictive and allow patient enrichment May provide additional insight into resistance mechanisms	Usually not validated as a surrogate of efficacy during early clinical development of an agent
Imaging	May allow early assessment of antitumor effect	May add little to response assessment Costly and time-consuming Difficult to combine results with multi-institutional trials

Danii et al. *Clin Cancer Res.* 2009;15(6)March15, 2009

D: Challenges and Opportunities

- Challenges
  - Information needed at the start of study
  - Blinding and use of Placebo
  - Combination trials
  - Determining the effect size
- New opportunities and trends
  - Precision Medicine
    - Microbiology and biomarkers, Targeted therapy
  - Designs of phases I-III
    - Basket Trials
    - Enrichment
    - Seamless trials

Information Needed at the Start of Study

- Investigator(s) need to know
  - Type and subtype of cancer
  - Adjuvant setting: May include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.
  - Metastatic disease?
  - Line of therapy? 1st? 2nd?, …..
  - Outcome of primary endpoint?
  - What is clinically meaningful gain in primary endpoint (effect size)?

Blinding and Use of Placebo

- Problems
  - Impossible to blind some therapies
  - Unmasking of blind by side-effects
  - Need to adjust doses
- Opportunities:
  - Oral drugs with fewer side-effects
- Placebos are rarely used in cancer treatment clinical trials. They are used when there is no standard treatment. Or, they may be used in a clinical trial that compares standard treatment plus a placebo, with standard treatment plus a new treatment

Combination Trials

- Drug approvals, drug labels, and drug marketing focus on effects from individual drugs.
- Many oncology regimens are combinations where the efficacy contribution of individual drugs may not be precisely defined.
  - One drug blocks the action of other
  - Synergy
  - Additive effect
  - No effect

Determining the Effect Size

- Determination of effect size is dependent on endpoint
- Statistically significant may not be clinically significant and vice versa
- May depend on meta analysis and need:
  - Multiple historical trials showing effect
  - Consistent large drug effect
  - However the Oncology reality:
    - Small historical drug effect in one or two trials
    - Leads to very small margin
- Drug combinations even more complicated

ASCO Recommended Targets for Meaningful CTs Goals

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

Ellis et al. *J Clin Oncol* 2014

Times Have Changed?

- From empirical Oncology to Molecular Oncology?
- All about Precision medicine
- Hope for ONE person trial (personalized medicine?
- Short-term trials: some methods to detect early effect

Types of Biomarkers

Prognostic	Predictive

• Information about disease outcome independent of treatment
• Example: EGFR mutation in NSCLC
  • Mutation + : better prognosis
  • Mutation - : worse prognosis
	• Information on disease outcome related to a specific treatment
	• Example: EGFR mutation in NSCLC
	  • Mutation + : ~70% probability of response to EGFR TKI therapy
	  • Mutation - : <5% probability of response to EGFR TKI therapy

Only predictive biomarkers can be used to indicate "which patients should be treated (or harmed) with which drug

New Trends/Opportunities

- Seamless designs: combining two trial phases.
- Basket design: Focus is on the tissue of origin. Looking at genetic landscape
- Population enrichment: placebo run-in, active control run-in, dose titration. Enrich the population at interim analysis based on biomarker or clinical endpoint response.
- Companion diagnostics: marker by treatment design with response adaptive allocation within strata.

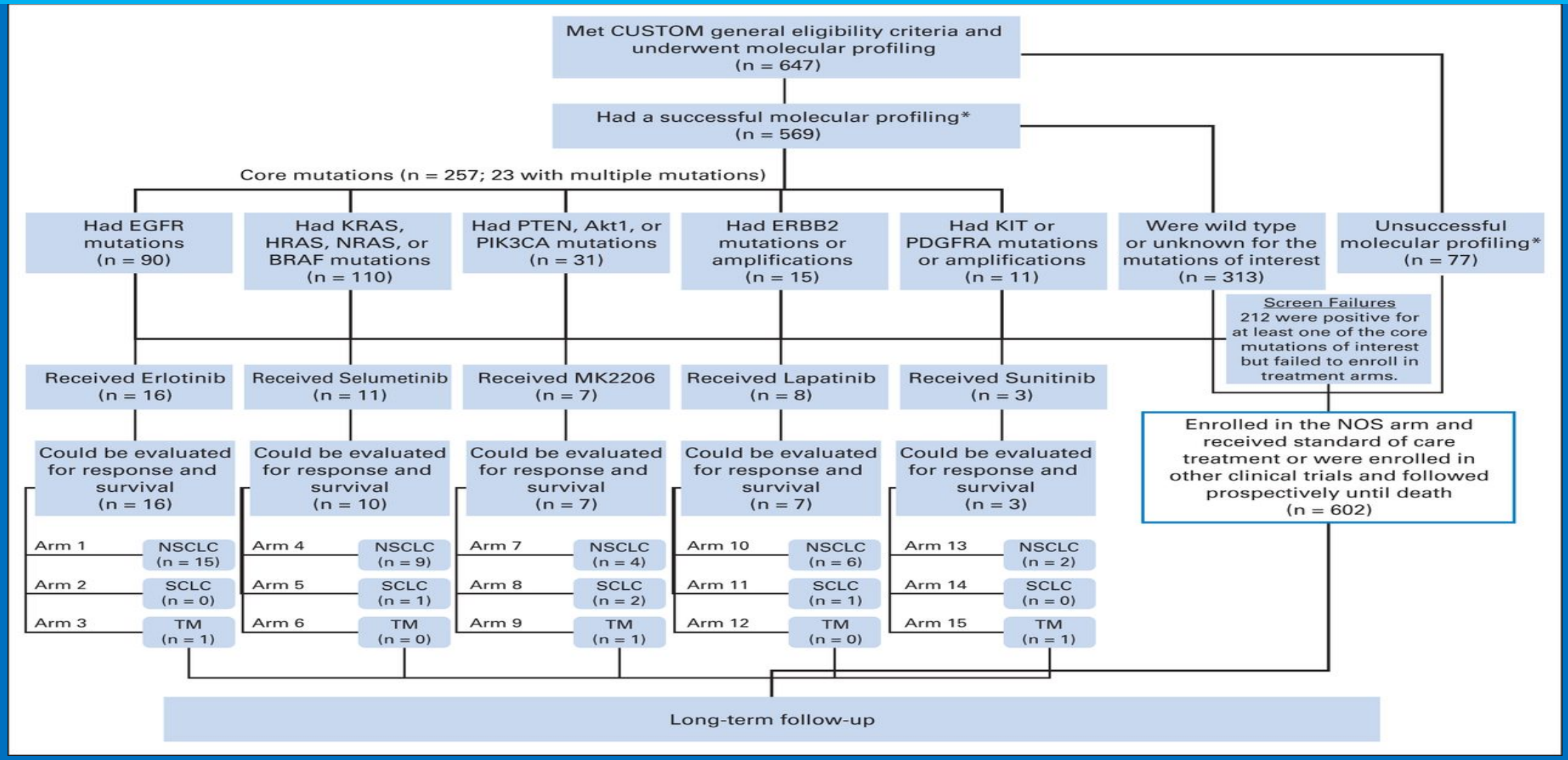
What is a Basket Trial?

- Trial design based on hypothesis that presence of a molecular marker predicts response to targeted therapy independent of tumor histology.
- Based on mutation status, patients assigned to specific treatment arm (or randomization to subset of treatments).
- Conducting several independent parallel phase trials.
- Hypothesis-driven strategy, incorporating precision medicine into trials even for rare mutations

Basket Trials

- Benefits
  - The ability to identify a favorable response to targeted therapy with a small number of patients
  - The ability to validate a clinical target
- Challenges:
  - Genetic classification and treatment may not always follow traditional approaches
    - HER2: common in breast cancer, but also in some lung cancers
    - BRAF: common melanoma, but also found in hairy cell leukemia, colon, lung, thyroid and brain cancers.
  - Hence, make-up of tumor may be very important or more important than site.
  - Identifying patients can be a challenge
- Evaluating target therapies is difficult when mutations are rare and span numerous diseases
  - Everolimus: mutations found so rare that trial was negative.

Example of Basket Trials structure



Ariel Lopez-Chavez et al. *JCO* 2015;33:1000-1007

Ramses Sadek, PhD

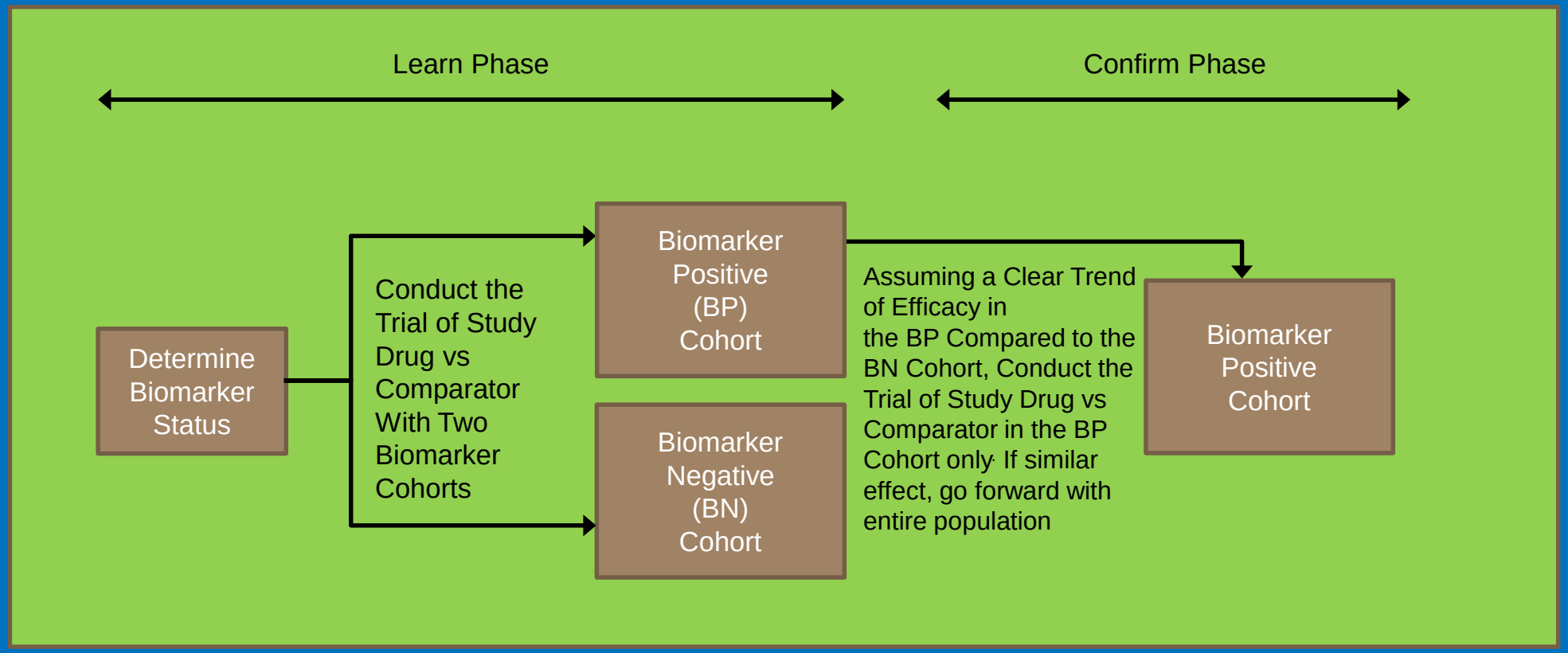
Seamless Designs

- Seamless design
  - A clinical trial design which combines into a single trial objectives which are traditionally addressed in separate trials (*operationally seamless*)
- Adaptive seamless design
  - A seamless trial in which the final analysis will use data from patients enrolled before and after the adaptation (*inferentially seamless*)
- Primary objective – combine "dose selection" and "confirmation" into a single trial
- Key Benefits: Efficiency; faster and more informed decision-making
- Key Challenges: Effective and Efficient Implementation

Enrichment Strategies

- Efficiency depends on strength of *a priori* information in relation to biomarker
- Known biomarker-effect relationship
  - Go straight to biomarker-selected design
- Less certain correlation or broader action of drug beyond biomarker
  - Include ALL; analyse by biomarker after N_1, validate activity in biomarker selected population in N_2: e.g., PDL1 inhibitor studies

Population Enrichment Design



Ananthakrishnan R et al. *Crit Rev Oncol Hematol*. 2013 Oct;88(1):144-53

Some Examples of Precision medicine trials

- Targeted Agent and Profiling Utilization Registry (TAPUR) Study – ASCO
- Molecular Analysis for Therapy Choice (MATCH) – NCI: use more than 20 study drugs or combinations, each targeting a specific gene mutation.
- SPY trials
- High level of collaboration

TAPUR study

- First ASCO trial – 10 to 15 drugs contributed by AstraZeneca, Bayer, Bristol-Myers Squibb, Lilly, Genentech, Merck, and Pfizer, in cohorts of up to 35 patients defined tumor type, genetic abnormality and drug.
- Instead of defining cancer by area of body (e.g. Breast cancer), advanced genomic testing is used to identify mutations that derive cancer's behavior. Patients may have same mutation though their cancer has formed in different area of the body.
- Design: Non-randomized, unblinded, multi-arm
- Outcomes : ORR (primary) using RACIST for solid tumor and Lugano Criteria for non-Hodgkin Lymphoma. OS (secondary)

TAPUR study

- TAPUR is testing drugs that the FDA has concluded are safe and effective to treat specific mutations in specific cancer types.
- The TAPUR study aims to learn whether using these drugs in other cancer types with the same mutations will also yield safe and effective therapies. Therefore, TAPUR focuses on the mutations and is open to a wide range of cancer types.
- **It is more inclusive.** Unlike studies with very rigid qualifications for eligibility, this trial is designed to include a wider patient population. As a result, TAPUR is learning from the experience of a wider array of cancer patients.
- Rather than base treatments on large populations of patients, the study looks at the individual patient's tumor. This is the future of cancer research. It changes the thought processes for how oncologists treat cancer."

TAPUR Study Arms

Arm	Intervention	Arm	Intervention
1. VEGFR	Axitinib	9. BRAFV600E	Cobimetinib
2.Bcr-abl, SRC, LYN, LCK	Bosutinib	10. OTCH1	Vismodegib
3. ALK, ROS1, MET	Crizotinib	11. KRAS, NRAS and BRAF	Cetuximab
4. CDKN2A, CDK4, CDK6	Palbociclib	12.Bcr-abl, SRC, KIT, PDGFRB, EPHA2, FyN, LCK,YES1	Dasatinib
5. CSF1R, PDGFR, VEGFR	Sunitinib	13. RET,VEGFR1/2/3,KIT, PDGFRβ, RAF-1, BRAF	Regorafenib
6. mTOR, TSC	Temsirolimus	14. BCRA1/BRCA2, ATM	Olaparib
7. EGFR	Erlotinib	15. POLE,POLD1, high mutational load	Pembrolizumab
8. ERBB2	Trastuzumab and Pertuzumab		

Selected References

- FDA IND application
- FDA Guide to enrichment trials.
- FDA Guidance:
  - *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
  - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
- NCI website
- I-Spytrials.org
- •Adjei A, Christian M, Ivy P. (2009). Novel Designs and End Points for Phase II Clinical Trials. *Clinical Cancer Research, 15*(6), 1866-1872.

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Additional slides

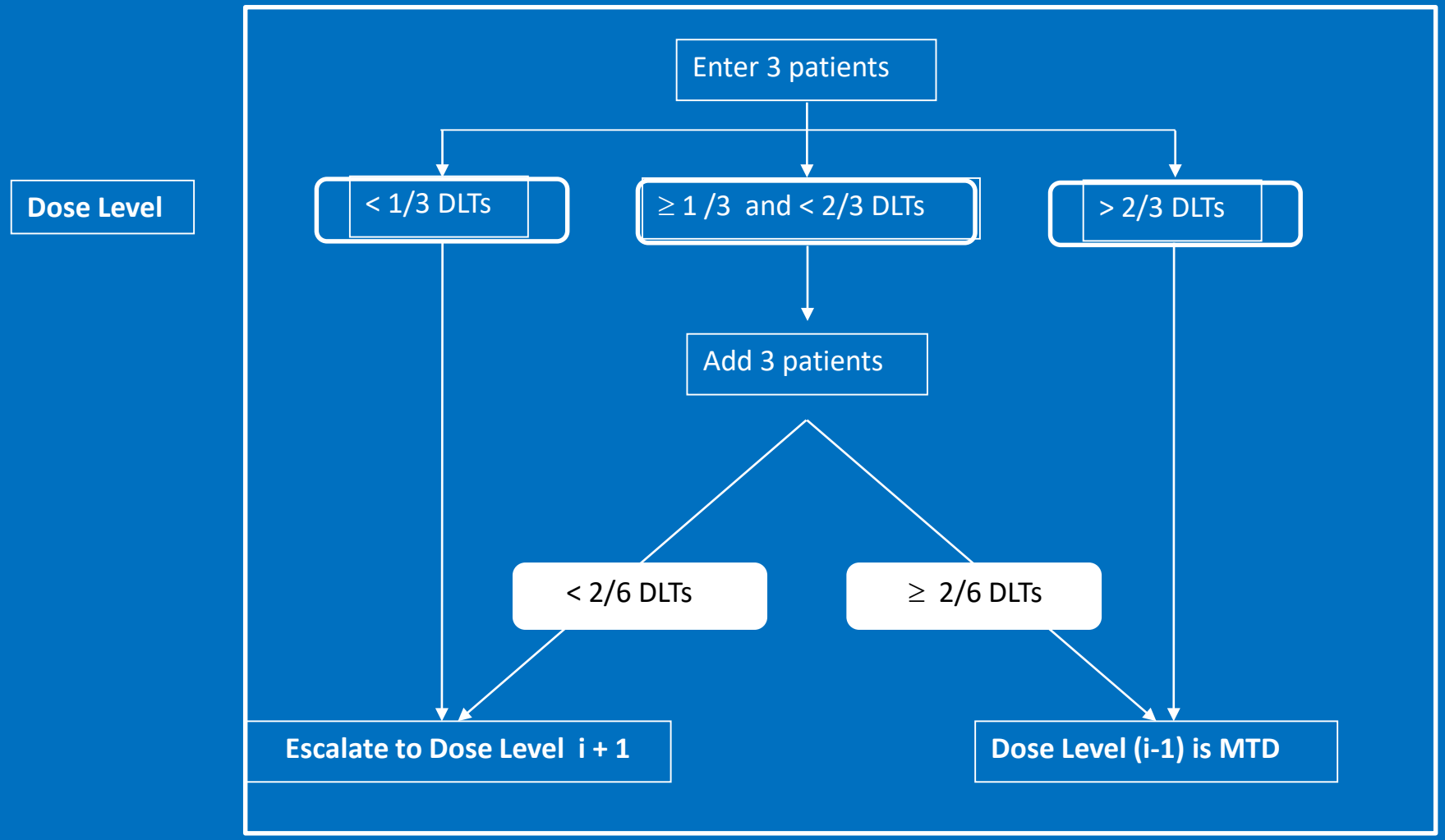
Phase I Oncology CT Goals

- Phase I Goals:
- "Find the dose that kill the tumor rather than the patient"
  - Define dose Limiting toxicity (DLT)
  - Define maximum tolerate dose (MTD)
  - Determine recommended phase II dose(s) (RP2D)
  - Start development of AE profile
  - Others:
    - Evaluate pharmacokinetics in terms of drug absorption, distribution, metabolism, excretion
    - Evaluate new treatment schedule
    - Evaluate new drug combination strategy

Phase I Oncology Trial Design

- Usually Open label, dose escalation, non-randomized
- 1. data driven design, examples are:
  - Classical 3+3 design and many modifications of it
  - Accelerated design: 1 patient per dose level until grade 2 AE is observed, then go to 3+3 design
  - Other modification of 3+3: (up and down designs)
  - Intra-patient dose escalation: escalate if subject tolerate, and if dose is proven safe then subjects at lower levels can be escalated to the safe level.
- 2. Model based design:
  - CRM, TITE-CRM ((TIme To Event) - Bayesian based models
    - TITE-CRM proved good for late toxicity.

Schema for 3+3 Design



Phase II and III CT Goals

- Phase II Goals: "treat the patient but expect no response- any promise?"
  - Evaluate activity
  - Further evaluate safety at MTD

  - Phase III Goals: "confirmatory"
    - Efficacy compared to standard therapy
    - Further evaluation of safety

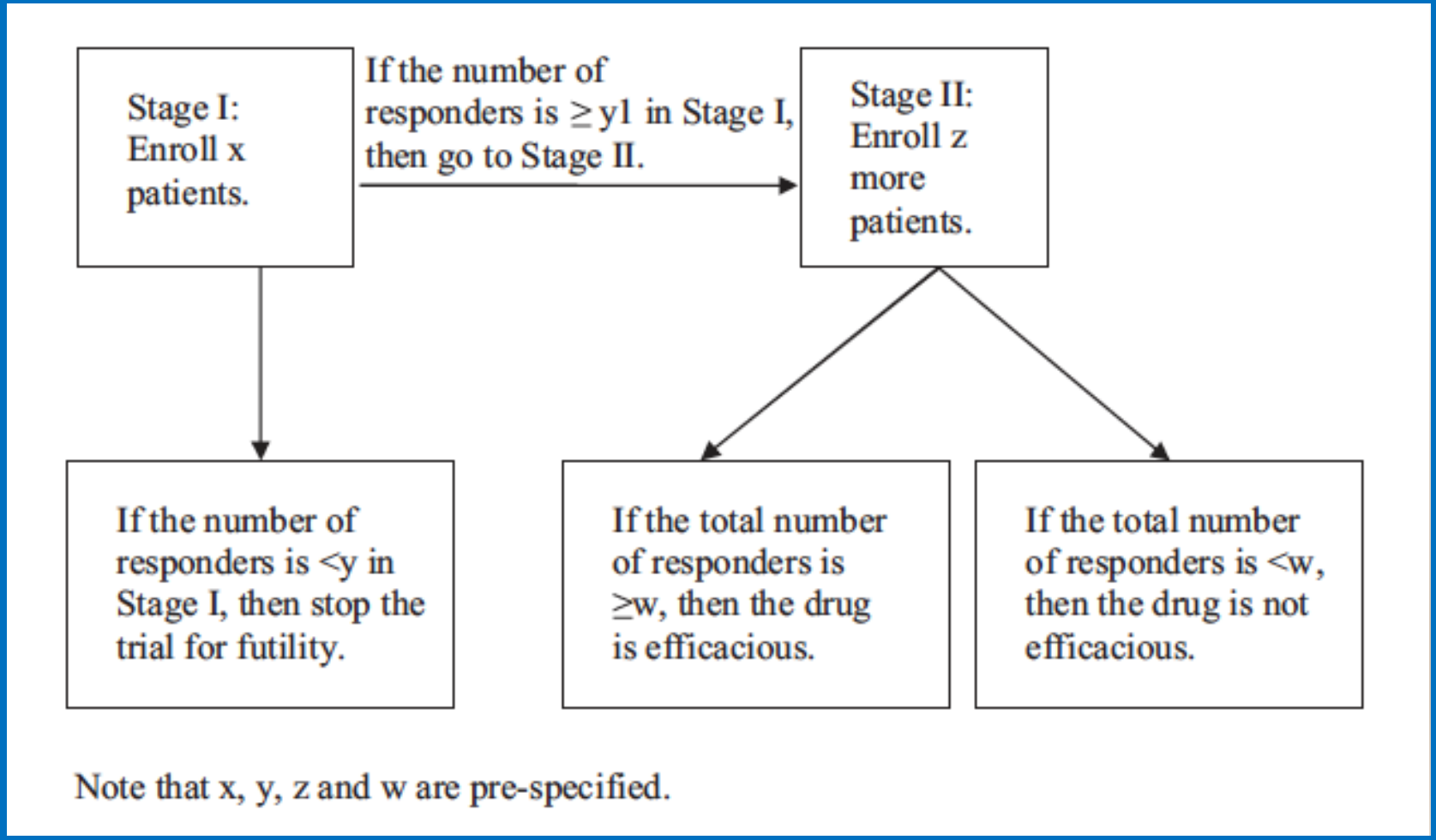
Examples of Phase II Designs

- Standard:
  - Two-stage with early stopping rule
    - Simon's (1989), Gehan's (1961), Fleming (1982)
- Low dose vs. higher dose of new agent
- Inactive vs agent (new agent alone or +placebo) Vs. (new agent + standard of care)
- Randomized discontinuation design:
  - Active agent for defined time frame then
  - If stable disease, then randomize to placebo or new agent.
  - Otherwise off study.
  - In case of progression on placebo, switch back to active agent.

Efficacy Endpoints

Phase II	Phase III
Complete Response (CR) Partial Response (PR) Response Rate (CR+PR) Stable Disease (SD) Progressive Disease (PD) Additional safety data	Overall survival (OS) Disease-free survival (DFS) Progression-free survival (PFS) Symptom control (PRO) Quality of life (QoL)

Classic Simon 2-Stage Single-Arm Study



Ananthakrishnan R et al. *Crit Rev Oncol Hematol*. 2013 Oct;88(1):144-53

PRO/QoL in Oncology Trials

- Direct measures of patient benefit, they can be considered independent endpoints
- PRO address more than just symptoms
- Specially useful in trials of drugs for patients with incurable cancers, in which one of the main goals is to improve palliation of symptoms
- Only 1/3 of phase 3 breast cancer trials registeries with US NIH have collected or are presently collecting PRO
- Calls to have PRO and QoL assessments for patients and caregivers.

Wilson et al. Lancet Oncol 2015

Seamless Phase I/II

- Seamless phase I/II, phase Ib:
- To identify optimal safe dose using single or multiple ascending dose combined with biomarker-based efficacy.
- Or dose escalation followed by cohort(s) with recommended Phase II dose(s).

Phase II/III Seamless Design Checklist

- The hypotheses are pre-defined and will not change
- There is positive data from proof-of-concept studies
- The remaining uncertainty primarily concerns dose
- The primary endpoint for confirmation is pre-specified and will be measured on all patients
- Patient population will stay the same in both phases
- The marketing formulation is available
- There is sufficient animal data to allow longer drug exposure: Phase II decision may be based on a biomarker believed to be predictive of the clinical endpoint for confirmation

The SPY Trials: Adaptive Breast Cancer CTs

- I-Spy 1 (Phase I Trial): 7 trial locations for accelerated expansion cohort enrollment to determine drug safety.
- I-SPY 2 (Phase II Trial):
  - Treating patients with stage 2-3 breast cancer at time of primary diagnosis using innovative design:
  - Administration of chemotherapy prior to surgery and use MRI to trach tumor response
  - Using adaptive design utilizing the response information from each patients through the study to help treat the next patient
  - Using the patient's tumor profile to assign targeted therapies best suited to tumor biology
  - The adaptive design enables testing of multiple agents creating efficiency and allowing drugs to be evaluated faster
  - The use of pathological completer response (pCR), the absence of residual invasive disease as an early surrogate marker of longer term outcomes of relapse free and overall survival.
  - 12 sites in 16 clinical study sites (in 11 states and Canada)

The SPY Trials

- I-Spy 3 (Phase III Trial:
  - International confirmatory trial using successful agents from SPY 2 to confirm the efficacy of the new treatments.
  - Targeted eligibility criteria for breast cancer subtype most likely to respond
  - Adaptive design to optimize sample size and maximize potential success

Collaborative

- As SPY 2, it uses master protocol and shared control arms to reduce time and cost
- Use parallel FDA, and EMA approval pathways. And works with sites across EU, Australia, Japan, and New Zealand.
- Collaboration with multiple companies: Medivation, abbvie, Amgen, Genentech, Merck, Plexxikon, and others.
- Collaborative efforts among academia investigators, and NCI, FDA, pharma, and biotech under the auspices of the foundation NIH biomarker consortium.